Is science getting closer to the brain center for male libido?

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A single hardwired brain circuit might be responsible for male sexual

drive, a new mouse study reports.

Researchers have singled out in lab mice a brain region that controls sexual interest, libido, mating behavior and pleasure, said senior researcher Dr. Nirao Shah, a professor of psychiatry and neurobiology at Stanford University School of Medicine, in California.

This region uses sensory input from the environment to recognize the sex of another mouse—"Aha, this is a female, maybe I can mate if she's willing," Shah said.

"That recognition is then transformed into the desire to mate and the act of mating by this circuit," he added. "Also, the circuit enables the behavior to be pleasurable so animals will seek to do it again, which is very important, because for a species to survive, animals need to reproduce."

While this study was in mice, Shah said similar brain structures have been found in other mammals—and perhaps even humans.

"There are analogous anatomical counterparts we think in the human brain, but of course their function in the human brain remains to be determined," he noted.

For their experiments, Shah's team used adult virgin male mice that had not seen a female mouse after being weaned at about 3 weeks of age. That way, the brain activity and behavior they observed would not have been shaped by social influences.

The researchers meticulously mapped the brain cells and connections that compose this particular circuit, called the preoptic area of the hypothalamus (POA).

Earlier work by the research team had found they could turn on and off male mice's recognition of an unfamiliar female mouse by manipulating neurons that communicate to the POA from the amygdala, which is the seat of human emotion.

The specific signals came from a part of the amygdala called the bed nucleus of the stria terminalis, or BNST.

"We had no reason to believe that this POA region would not only control the act of mating, but also regulate the desire to mate or regulate the pleasurable feelings elicited by mating," Shah said.

"In principle, those three aspects of sexual behavior—the act of mating, the physical act itself, the urge to mate and the pleasure that accompanies it—those could be embodied in different brain regions," he added. "But what we found is that the POA has these attributes."

In this new study, the researchers zeroed in on a small set of genetically distinct BNST neurons that secrete a slow-acting signaling protein, or peptide, called Substance P.

The scientists also found another small set of neurons in the POA that carried receptors for Substance P, essentially forming a connection with the BNST neurons.

The POA neurons ramped up their activity when stimulated by the Substance P-secreting BNST neurons. And about 10 to 15 minutes after that happened, male mice would go through their full sequence of mating behavior—mounting, penetration and ejaculation.

Substance P sensitizes the POA neurons so they become increasingly active, the researchers concluded.

Directly infusing the peptide to the POA accelerated mating behavior; in fact, direct activation of the circuit even led to mating with inanimate objects, the findings showed.

Stimulation of the POA also cut short the mice's refractory period, or the stretch of recovery time required before full sexual drive and capability is restored after ejaculation.

For the mice used in this study, the normal refractory period is five days. But directly stimulating the POA with Substance P prompted male mice that had just ejaculated to immediately repeat their sexual mating routine.

"It took one second or less for them to resume sexual activity," Shah said in a news release. "That's a more than 400,000-fold reduction in the refractory period."

On the other hand, blocking the POA completely eliminated the mating urge in male mice, Shah said.

"When we switch off the center, the POA in the male mouse, he simply stops mating," Shah said. "Even if he has a willing female in his cage. Even if there's no danger. Even if there's ample food. He just stops mating."

There seem to be no other effects researchers can see, he said.

"He walks about normally. There's no problems in other behaviors like aggression. He will still fight with males, because they're competitors. He simply doesn't mate," Shah said.

Further, Substance P receptor-containing neurons in the POA connect to two downstream brain centers that are known to be critical to voluntary

movement and experiencing or anticipating pleasure.

"Importantly, similar structures exist in creatures less complex than mice such as birds, that are not even mammals," Shah said.

"In monkeys, studies done some years ago showed that switching on one of the centers that we worked on in the mouse actually does elicit male mating behavior, suggesting a functional correspondence between the mouse and the monkey counterpart in the brain," he added.

"So there seems to be anatomical correspondences between birds, mice, monkeys, humans and these brain regions, and there seems to be functional correspondence as well between mice and monkeys," Shah said.

The findings could lead to drugs that tamp down the sex circuitry in the brains of men with hyperactive sex drives. Alternatively, new treatments might boost sex drive in men who suffer from a lack of desire.

"If these centers exist in humans—and now we know where to look—it should be possible to design small molecules that can be used to regulate these circuits," Shah said

"But whether this is feasible is unknown because first we would need to identify these centers in the human brain and, moreover, regulating libido is enormously complex in humans with lots of social, political, ethical and other considerations that need to be addressed prior to thinking about any such approach," he added.

A sex-stimulating drug aimed at the human equivalent of the POA would act very differently than erectile dysfunction drugs like Viagra, Shah said.

Instead of stimulating blood flow in the small blood vessels, such drugs would directly act upon the specific brain area that controls the male libido, he explained.

Shah's group is also trying to find equivalent brain circuits in females.

The new study was published online Aug. 11 in the journal *Cell*.

More information: Daniel W. Bayless et al, A neural circuit for male sexual behavior and reward, *Cell* (2023). DOI: 10.1016/j.cell.2023.07.021